ORIGINAL INVESTIGATION

Utility of Scintigraphic Methods in Patients With Fever of Unknown Origin

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Background: We assessed the utility of scintigraphy with indium 111–labeled polyclonal human IgG scintigraphy in patients with fever of unknown origin that fulfilled the criteria of temperature of 38.3°C or more for at least 3 weeks and no diagnosis during 1 week of hospital admission. We compared the utility of this technique with results of scintigraphic techniques reported in the literature.

Methods: Data for all patients seen at our university hospital in whom ^{111}In-IgG scanning was performed were analyzed and checked for the criteria for fever of unknown origin. The literature on the utility of scintigraphic techniques in patients with fever of unknown origin was reviewed.

Results: We studied 24 patients with fever of unknown origin. In 13 patients, focal ^{111}In-IgG accumulation was observed. In nine (38%) of those, the positive ^{111}In-IgG scintigram led to the final diagnosis; in the other four patients (17%), the scintigraphic findings were not helpful. In the 11 patients with negative ^{111}In-IgG scans, extensive diagnostic workup produced no infection as the final diagnosis in nine patients (38%), one had an abscess in a renal cyst that was detected several months later, and in the other the cause of fever was an infected intravenous line. The overall sensitivity and specificity of ^{111}In-IgG scintigraphy were 81% and 69%, respectively. The positive predictive value was 69% and the negative predictive value was 82%.

Conclusions: Our results show that ^{111}In-IgG scintigraphy significantly contributed to the diagnostic process in patients with fever of unknown origin. A positive scan increased the likelihood of finding the cause of the fever, and a negative scan ruled out an inflammatory component with a high degree of certainty. These data compare favorably with data in the literature concerning other radiopharmaceuticals; a larger prospective evaluation of this technique is indicated.

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FEVER OF unknown origin (FUO) has been defined by Petersdorf and Beeson[1] as a febrile illness of more than 3 weeks' duration, documented temperature higher than 38.3°C on at least three occasions, and uncertain diagnosis after 1 week of diagnostic workup in the hospital. Currently, a variety of diagnostic imaging procedures, including radiography, magnetic resonance imaging, ultrasonography, and scintigraphy, are potentially useful in patients with FUO.

Scintigraphic imaging, including gallium 67,[2-9] white blood cells (WBCs) labeled with indium In 111,[10-12] and, most recently, technetium Tc99m–labeled BW250/183, an antigranulocyte monoclonal antibody of murine origin,[13] has been applied in patients with FUO to detect infectious and other inflammatory foci. A positive scintigram enhances the likelihood of establishing a final diagnosis.[8]

A relatively new and potentially useful technique for this indication is indium 111–labeled polyclonal human IgG scintigraphy. Recently, the utility of ^{111}In-IgG scintigraphy in the evaluation of various types of focal inflammation and infection has been studied. Reports have been published in the literature on bone and joint infections[14,15] and abdominal,[16] pulmonary,[17] and vascular[18] lesions. This technique is also applicable in granulocytopenic patients.[19] Since ^{111}In-IgG is a convenient and safe radiopharmaceutical, comparing favorably with other scin-

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PATIENTS AND METHODS

PATIENTS

Records of all patients who underwent ^{111}In-IgG scintigraphy in our hospital were reviewed for FUO.[1] Twenty-four patients (11 women and 13 men; mean age, 51 years; median, 52 years) fulfilled the criteria for FUO. From our studies of FUO carried out during the same period, we found that 45% of the patients with FUO had undergone ^{111}In-IgG scintigraphy.

All patients underwent full biochemical and appropriate further investigations, including extensive negative microbiologic methods, which failed to establish a diagnosis within 1 week of admission. These investigations varied from patient to patient; no protocol was followed. The median follow-up of these patients was 216 days (range, 2 to 1500 days).

The final diagnosis was made by the patients' physicians and checked by one of us (E.M.H.A.K.).

RADIOPHARMACEUTICAL

Human nonspecific polyclonal IgG (Sandoglobulin, Sandoz AG, Nürnberg, Germany) was conjugated to diethylenetriamine pentaacetic bicyclic anhydride according to the method described by Hnatowich et al[20] and labeled with indium 111 (indium [^{111}In] chloride, Medgenix Diagnostics, Fleurus, Belgium). Labeling efficiency was always greater than 95%. A dose of 1 to 2 mg of IgG labeled with 75 MBq of ^{111}In was injected intravenously.

IMAGING PROCEDURES

Exclusion criteria for ^{111}In-IgG scintigraphy were agammaglobulinemia, selective IgA deficiency, and a history of severe adverse reactions after intravenous or intramuscular administration of human IgG. Pregnant or lactating women were also excluded from this study.

Scintigraphic images were obtained with a gamma camera (Siemens Orbiter, Siemens Inc, Hoffman Estates, Ill) connected to an image processor (Scintiview, Siemens Inc). All images were collected in digital format in a 256×256 matrix. A medium-energy parallel-hole collimator (173-keV peak, 15% symmetric window; 247-keV peak, 15% symmetric window) was used.

The ^{111}In-IgG images were acquired 4, 24, and 48 hours after injection for a preset time of 5, 7.5, and 10 minutes, respectively. At least once, 24 hours after injection, spot views of the total body were obtained. Single-photon-emission computed tomographic images were recorded when necessary for more definite localization in three dimensions of areas with increased uptake.

All images were interpreted by three observers, "blinded" to the results of the verification procedures. Disagreements were resolved by consensus opinion. Hyperemic noninflamed lesions may initially show some uptake but no further accumulation of ^{111}In-IgG with time.[21] These scans were interpreted as equivocal and not pathologic. An ^{111}In-IgG scan was interpreted as positive only if consistent, focally increasing accumulation could be noted over time. An ^{111}In-IgG scintigram was considered "true positive" only when this imaging procedure was considered helpful in diagnosis.

The results of the scintigraphic findings were verified by clinical, radiographic, and ultrasonographic methods and preferably by microbiologic methods.

STATISTICS

Differences between groups were analyzed by the Mann-Whitney *U* test or Student's *t* test, when necessary.[22]

tigraphic techniques, we studied its diagnostic utility in patients with FUO.

RESULTS

In 13 (54%) of 24 patients, focal accumulation of activity increasing with time was observed. In nine patients (38%), scintigraphy was diagnostically helpful (**Table 1**); in eight of these, inflammatory or infectious foci were identified as the cause of the fever (**Figure 1** and **Figure 2**). In four other patients (17%), a positive ^{111}In-IgG scintigram did not lead to the final diagnosis (Table 1).

Table 1 also shows the data for the remaining 11 patients, in whom a negative or equivocal ^{111}In-IgG scintigram was obtained. In six of those patients, extensive workup disclosed no diagnosis; follow-up from the start of fever varied from 224 to 929 days (median, 515 days). In two patients a malignant neoplasm most probably was the cause of fever, and one patient had positive blood cultures with *Salmonella enteritidis* serotype *paratyphi A*. The two remaining patients had infections as the cause of the fever despite negative IgG scintigrams; one had an infected renal cyst, diagnosed 3 months after the negative ^{111}In-IgG scan, and the other had an infected central venous catheter.

If we considered results of ^{111}In-IgG scintigraphy as true positive only when this imaging procedure led to the diagnosis, sensitivity was 82%, specificity was 69%, and positive and negative predictive value was 69% and 82%, respectively.

Comparison of the erythrocyte sedimentation rate of patients with positive scans (mean±SD, 80.8±43.0 mm/h) with that of patients with negative scans (mean±SD, 70.5±47.5 mm/h) yielded no significant difference (P=.66). Likewise, WBC counts of patients with positive scans (mean±SD, 9.9±5.7×10^9/L) and patients with negative scans (mean±SD, 8.0±3.3×10^9/L) did not differ significantly (P=.38).

Comparison of the groups with positive and negative ^{111}In-IgG scans showed that a positive scan significantly increased the likelihood of reaching a diagnosis: in 11 (85%) of 13 patients with a positive scan, a final diagnosis was made, compared with only five (45%) of 11 patients with a negative scan (P=.05).

COMMENT

From this study, it can be concluded that ^{111}In-IgG scintigraphy is a promising technique in the workup of patients with FUO, as indicated by an overall sensi-

Table 1. Characteristics of Patients According to Results of Indium In 111 IgG Scans*

Patient/ Age, y/ Sex	ESR, mm/h	Clinical Data	Leukocytes, $\times 10^9$/L	Fever Duration, wk	Localization of Uptake	Final Diagnosis	Additional Investigations†
				True-Positive Scans			
1/81/F	93	Arthritis of knee, heart murmur	11.4	4	Right knee	Tuberculous arthritis, spondylodiskitis	Puncture, C
2/67/F	132	Lumbar pain	8.5	8	Left hip, back	Spondylodiskitis, arthritis with Group B *Streptococcus* and *Propionibacterium acnes*	B, C, X
3/23/F	40	Lymphadenopathy, abdominal pain, arthritis	12.7	7	Right lower abdomen	Crohn's disease	Colonoscopy
4/65/M	140	No abdominal complaints	26.5	22	Right lower abdomen	Ileum metastasis of surgically cured lung cancer	X, CT, S, PE
5/63/M	90	No abdominal complaints, steroids	5.7	3	Right lower abdomen	Abscess with *Escherichia coli* after appendicitis	US, S
6/33/M	70	Recurrent abdominal pain, no diarrhea	7.6	7	Ascending colon	Ulcerative colitis	X, colonoscopy, PE
7/48/M	72	Polyarthritis, pleural effusion	5.4	8	Both lungs, left hip, knee	Nonclassifiable noninfectious inflammatory lung disease, culture-negative periostitis	Open lung B, CT, US, C, B, blood, DSA
8/46/M	136	Low thoracic pain, pleural effusion	6.6	11	Right lung	Pleural empyema and spondylitis with *Staphylococcus aureus*	CT, X, B, US, C
9/63/F	20	Polyarthritis, diarrhea without blood	10.9	20	No activity in kidney	Hydronephrosis in colon cancer, *E coli* in urine	US, X, colonoscopy, S, PE
				False-Positive Scans			
10/49/M	50	Fatigue, recurrent fever for 5 y	8.1	53	Both hips	Aseptic necrosis of hips, no cause of fever found	X, Tc bone scan, US
11/61/M	120	Nonspecific complaints, pain in right hip from coxarthrosis, spontaneous recovery from fever	8.5	7	Right hip	No diagnosis	S, C
12/25/F	75	Abdominal pain, extreme weight loss	3.9	4	Nose, left axilla	Systemic lupus erythematosus, nonspecific lymphadenopathy of axilla	B, CT, **blood**
13/44/F	12	Dyspnea, heart murmur, spontaneous recovery from fever	13.4	23	Ascending colon	No diagnosis	Blood, C

(continued)

tivity of 82%. The specificity was 69%. These results compare favorably with data in literature dealing with other radiopharmaceuticals (**Table 2**). Most scintigraphic studies in FUO have been performed with gallium citrate Ga 67[2-8,10,23] and ^{111}In-WBCs.[11-13,24] For scintigraphic studies with Ga 67, sensitivity ranged from 75% to 100% and specificity varied widely, ranging from 38% to 100%. In ^{111}In-WBC scintigraphy, sensitivity and specificity appeared to be much higher, ranging from 90% to 100% and 84% to 86%, respectively. When these data are compared, ^{111}In-WBC scintigraphy seemed to perform somewhat better than Ga 67 scintigraphy and ^{111}In-IgG scintigraphy. However, few studies adhere to the criteria for FUO formulated by Petersdorf and Beeson[4-7,11,12]; some even include postoperative patients with fever, who often have a localized abscess.[4,5] Those results cannot be extrapolated to those patients with classic FUO, making comparison of these data somewhat hazardous. Moreover, in most other studies, only a selection of patients with FUO was included.[3,5,8,10,11,13,22,23]

Knockaert et al[8] found in patients with FUO that a positive Ga 67 scintigram increased the chances of reaching a final diagnosis; 77% of patients with positive scans in contrast to 34% of those with negative scans were given a final diagnosis. This is in agreement with our findings with the use of ^{111}In-IgG: a final diagnosis was made in 10 (77%) of 13 patients with a positive scan and in five (45% of 11 patients with a negative scan. In previous experience with more than 1000 patients studied with ^{111}In-IgG for a variety of indications,[14,21] this technique had a high diagnostic yield, and in comparison with Ga 67 and ^{111}In-WBC scintigraphy, it has many advantages. First, unlike gallium citrate Ga 67 and technetium Tc99m hexamethylpropyleneamine oxime–labeled WBCs, ^{111}In-IgG is not secreted in the normal bowel, leading to better detection of abdominal infections or inflammation. In addition, the radiation burden of gallium citrate Ga 67 is higher than that of ^{111}In-IgG, ie, an effective dose equivalent of 27 and 15 mSv, respectively.[21,25] In chronic infection, sensitivity of labeled WBC scintigraphy might be limited by the absence of granulocyte influx in this type

Table 1. Characteristics of Patients According to Results of Indium In 111 IgG Scans* (cont)

Patient/ Age, y/ Sex	ESR, mm/h	Clinical Data	Leukocytes, $\times 10^9$/L	Fever Duration, wk	Localization of Uptake	Final Diagnosis	Additional Investigations†
				True-Negative Scans			
14/25/F	89	Heart murmur; Indonesian travel	6.1	6	Equivocal (pelvis)	*Salmonella* sepsis, prompt response to antibiotics	X, blood, **C**
15/77/M	112	Cough, diarrhea; artificial heart valves	7.4	17	None	Hodgkin's disease and lung cancer	S, **B, bronchoscopy**
16/62/M	96	Fatigue; spontaneous recovery after 4 mo	10.0	13	None	No diagnosis	BM, CT, C, US, blood
17/52/M	40	Fatigue, slight weight loss; pigeon fancier; spontaneous recovery after 10 mo	5.5	12	Equivocal (right lower abdomen)	No diagnosis	X, B, CT, B, US, C
18/46/M	140	Myalgia of legs, fatigue, anorexia	5.5	30	Equivocal (lungs)	Acute leukemia	CT, US, BM, **bone biopsy**
19/63/F	112	Fatigue, lumbar pain, transient diarrhea; spontaneous recovery after 4 mo	11.1	3	None	No diagnosis	US, CT, X, B, blood, C
20/53/F	14	Persistent recurrent fever for >4 y	4.6	88	None	No diagnosis	MR, CT, US, B, X, blood, C
21/35/M	5	Tick bite; recurrent fever with headache; spontaneous recovery after 1 y	4.4	51	None	No diagnosis	CT, X, B, C, blood, US
22/27/M	4	Fatigue; spontaneous recovery after 10 mo	7.1	18	Equivocal (colon)	No diagnosis	US, colonoscopy, C, blood
				False-Negative Scans			
23/54/F	93	Heart murmur, kidney transplant, renal cysts	11.7	5	None	Infected renal cyst, culture negative after use of several antibiotics	**S, C**
24/68/F	71	Scleroderma, heart murmur, renal failure	14.5	5	None	Infected central catheter with *Staphylococcus epidermidis*	CT, X, blood, US, **C**

*US indicates ultrasound; CT, computed tomography; B, biopsy; C, culture; S, surgery; MR, magnetic resonance imaging; X, x-ray; BM, bone marrow aspiration; PE, pathologic examination; DSA, digital subtraction angiography; and Tc, technetium.

†Investigations performed to verify the diagnosis are shown in boldface. For true-positive scans, all additional investigations were performed for verification.

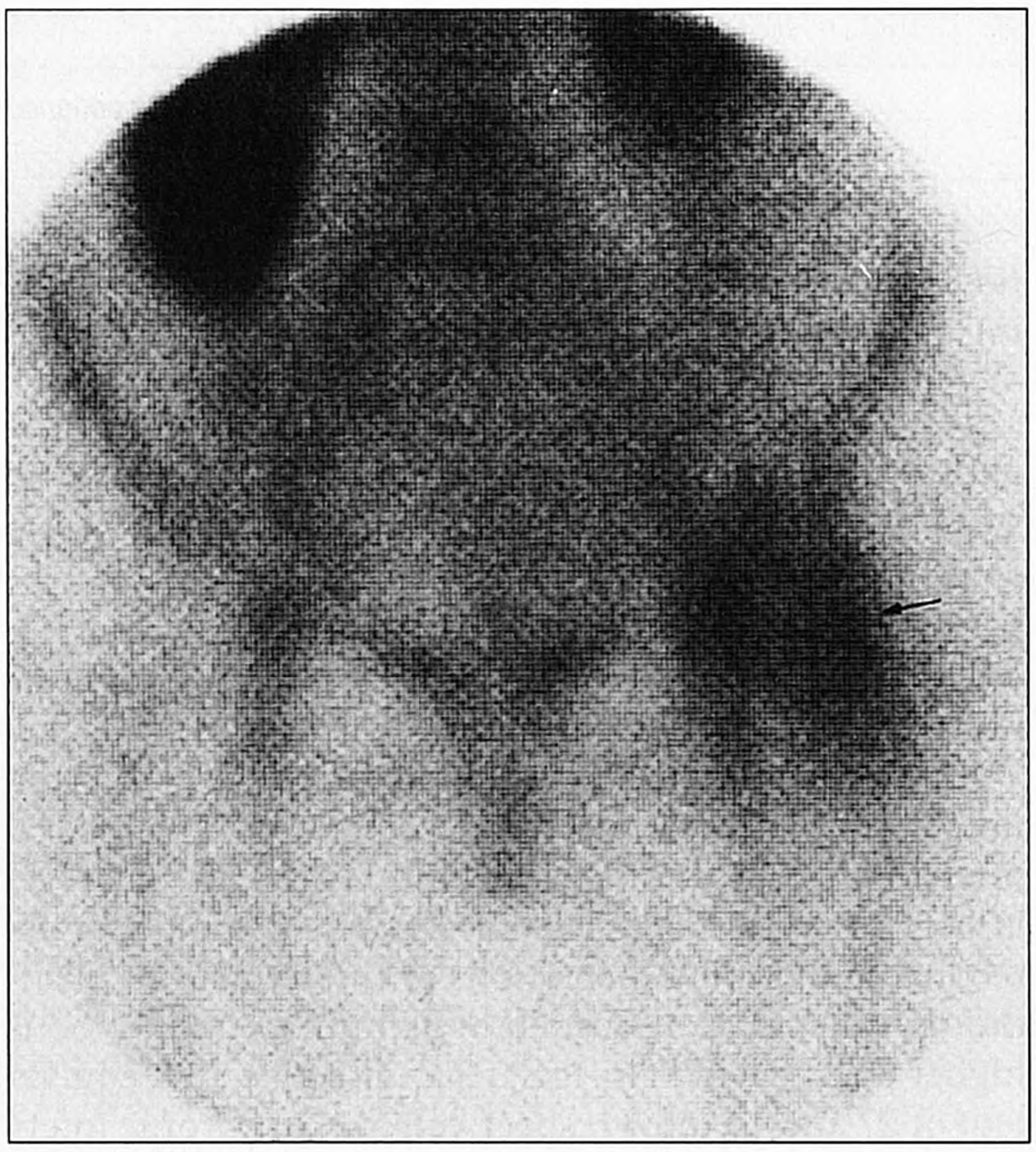

Figure 1. *Patient 2. Abnormal uptake in the left hip and back (arrow) caused by spondylodiskitis.*

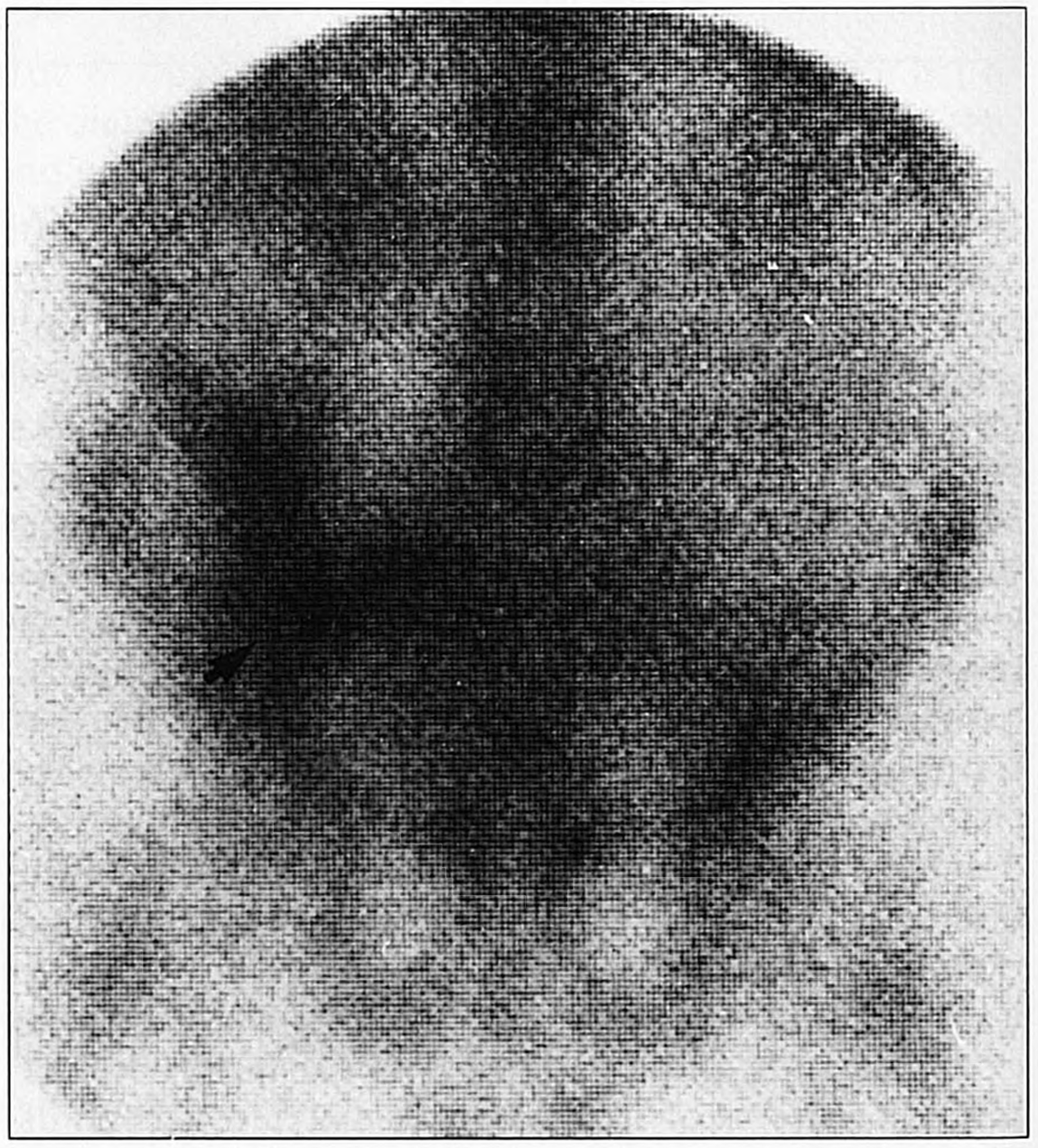

Figure 2. *Patient 3. Abnormal uptake in the right lower abdomen (arrow) caused by Crohn's disease.*

Table 2. Reports on Diagnostic Value of Scintigraphy in Patients With FUO*

Source, y	Scan	N	Scan Result, No. (%) TP	FP	TN	FN	Sensitivity, %	Specificity, %	Remarks
Nakamura et al,[2] 1990	Ga 67	49	8 (16)	17 (35)	. . .	. . .	. . .	. . .	Abstract
Misaki et al,[3] 1990	Ga 67	56	23 (41)	10 (17)	19 (35)	4 (7)	85	65	Selected group, abstract
Hilson and Maisey,[4] 1979	Ga 67	61	47 (77)	3 (5)	11 (18)	0 (0)	100	79	No criteria for FUO, also postoperative patients
Teates and Hunter,[5] 1975	Ga 67	42	9 (21)	5 (11)	25 (61)	3 (7)	75	83	Selected group, no criteria for FUO
Suga et al,[6] 1991	Ga 67	36	17 (47)	0 (0)	15 (42)	4 (11)	80	100	Retrospective, selected, other criteria for FUO
Habibian et al,[7] 1975	Ga 67	22	12 (54)	5 (22)	3 (15)	2 (9)	86	38	Also postoperative patients, no definition of FUO
Knockaert et al,[8] 1989	Ga 67	54	14 (26)	8 (15)	28 (51)	4 (7)	78	78	Criteria for FUO of Petersdorf, selected group
Larson et al,[23] 1982	Ga 67	40	10 (25)	9 (23)	18 (45)	3 (7)	77	67	Criteria for FUO of Petersdorf, selected group, other definition of true positive
Knockaert et al,[9] 1994	Ga 67	145	42 (29)	40 (28)	54 (37)	9 (6)	82	57	Criteria for FUO of Petersdorf, selected group, retrospective
Schmidt et al,[10] 1987	In 111 WBCs	32	7 (21)	4 (13)	21 (66)	0 (0)	100	84	Criteria for FUO of Petersdorf, selected group
Syrjälä et al,[11] 1987	In 111 WBCs	68	19 (28)	7 (10)	40 (59)	2 (3)	90	85	Other criteria for FUO, selected group
McDougall et al,[12] 1979	In 111 WBCs	13	3 (24)	1 (7)	9 (69)	0 (0)	100	90	No criteria for FUO mentioned, selected group
Davies and Garvie,[24] 1990	In 111 WBCs	28	3 (11)	5 (18)	18 (64)	2 (7)	71	86	Criteria for FUO of Petersdorf, selected group, retrospective
Becker et al,[13] 1993	Tc anti-NCA	34	8 (24)	1 (3)	13 (38)	12 (35)	40	92	Criteria for FUO of Petersdorf, selected group, retrospective
Present study	In 111 IgG	24	9 (38)	4 (17)	9 (38)	2 (8)	82	69	Criteria for FUO of Petersdorf, selected group, retrospective

**FUO indicates fever of unknown origin; TP, true positive; FP, false positive; TN, true negative; FN, false negative; Ga 67, gallium citrate Ga 67; In 111, indium In 111; Tc, technetium; WBCs, white blood cells; and NCA, nonspecific cross-reaching antigen.*

of infection.[26] In a prospective comparative study in subacute infections, with the use of ^{111}In-WBC and ^{111}In-IgG scintigraphy, Oyen et al[17] found a higher diagnostic accuracy of ^{111}In-IgG scintigraphy.

The need to draw blood and to isolate and label leukocytes makes ^{111}In-WBC and ^{99m}Tc-WBC scintigraphy more time consuming, complicated, and costly than ^{111}In-IgG scintigraphy. It takes 3 hours to prepare the radiopharmaceutical, and not every department of nuclear medicine has the facilities to label leukocytes. Of major concern are the handling of blood and the possibility of administering the cells to the wrong patient.[27] There is a limitation to the use of all scintigraphic techniques, including ^{111}In-IgG: lesions in organs with relatively high physiologic uptake, eg, liver, heart, spleen, and kidneys, can be missed. Because of these advantages and the high diagnostic yield, ^{111}In-IgG scintigraphy may become the first choice in scintigraphic investigations in patients with FUO.

Since this study, like all studies on scintigraphic methods in FUO, is retrospective, the exact role of ^{111}In-IgG scintigraphy in the diagnostic process of patients with FUO is unknown. Prospective studies are necessary to provide such additional information.

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